Long-term results of intensified, N-terminal-pro-B-type natriuretic peptide-guided versus symptom-guided treatment in elderly patients with heart failure: five-year follow-up from TIME-CHF

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Abstract: BACKGROUND Therapy guided by N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels may improve outcomes in patients with chronic heart failure (HF), especially in younger patients with reduced left ventricular ejection fraction. It remains unclear whether treatment effects persist after discontinuation of the NT-proBNP-guided treatment strategy. METHODS AND RESULTS Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure randomized 499 patients with HF aged 60 years with left ventricular ejection fraction 45% to intensified, NT-proBNP-guided versus standard, symptom-guided therapy into prespecified age groups (60-74 and 75 years) during 18 months. A total of 329 patients (92%) alive at 18 months agreed to long-term follow-up. HF medication was intensified to a larger extent in the NT-proBNP-guided group. During long-term, NT-proBNP-guided therapy did not improve hospital-free (primary end point: hazard ratio, 0.87; 95% confidence interval, 0.71-1.06; P=0.16) or overall survival (hazard ratio, 0.85; 95% confidence interval, 0.64-1.13; P=0.25) but did improve HF hospitalization-free survival (hazard ratio, 0.70; 95% confidence interval, 0.55-0.90; P=0.005). Patients aged 60 to 74 years had benefit from NT-proBNP-guided therapy on the primary end point and HF hospitalization-free survival, whereas patients aged 75 years did not (P<0.10 for interaction). In landmark analysis, there was no regression to the mean after cessation of the NT-proBNP-guided strategy. More intensified HF medication at month 12 was associated with better long-term HF hospitalization-free and overall survival. CONCLUSIONS Intensified, NT-proBNP-guided therapy did not improve the primary end point compared with symptom-guided therapy but did improve HF hospitalization-free survival. Within the subgroup of patients aged 60 to 74 years, it improved clinical outcome including the primary end point. These effects did not disappear after cessation of the NT-proBNP-guided strategy on the long-term. This is possibly attributable to a more intensified HF medical therapy in the NT-proBNP-guided group. CLINICAL TRIAL REGISTRATION URL: http://www.isrctn.org. Unique identifier: ISRCTN43596477.

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Long-Term Results of Intensified, N-Terminal-Pro-B-Type Natriuretic Peptide–Guided Versus Symptom-Guided Treatment in Elderly Patients With Heart Failure

Five-Year Follow-Up From TIME-CHF

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Background—Therapy guided by N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels may improve outcomes in patients with chronic heart failure (HF), especially in younger patients with reduced left ventricular ejection fraction. It remains unclear whether treatment effects persist after discontinuation of the NT-proBNP–guided treatment strategy.

Methods and Results—Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure randomized 499 patients with HF aged ≥60 years with left ventricular ejection fraction ≤45% to intensified, NT-proBNP–guided versus standard, symptom-guided therapy into prespecified age groups (60–74 and ≥75 years) during 18 months. A total of 329 patients (92%) alive at 18 months agreed to long-term follow-up. HF medication was intensified to a larger extent in the NT-proBNP–guided group. During long-term, NT-proBNP–guided therapy did not improve hospital-free (primary end point: hazard ratio, 0.87; 95% confidence interval, 0.71–1.06; P=0.16) or overall survival (hazard ratio, 0.85; 95% confidence interval, 0.64–1.13; P=0.25) but did improve HF hospitalization-free survival (hazard ratio, 0.70; 95% confidence interval, 0.55–0.90; P=0.005). Patients aged 60 to 74 years had benefit from NT-proBNP–guided therapy on the primary end point and HF hospitalization-free survival, whereas patients aged ≥75 years did not (P<0.10 for interaction). In landmark analysis, there was no regression to the mean after cessation of the NT-proBNP–guided strategy. More intensified HF medication at month 12 was associated with better long-term HF hospitalization-free and overall survival.

Conclusions—Intensified, NT-proBNP–guided therapy did not improve the primary end point compared with symptom-guided therapy but did improve HF hospitalization-free survival. Within the subgroup of patients aged 60 to 74 years, it improved clinical outcome including the primary end point. These effects did not disappear after cessation of the NT-proBNP–guided strategy on the long-term. This is possibly attributable to a more intensified HF medical therapy in the NT-proBNP–guided group.

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Key Words: aging ■ heart failure ■ pro-brain natriuretic peptide (1–76) ■ prognosis ■ type-B natriuretic peptide

Heart failure (HF) therapy guided by natriuretic peptides, that is, N-terminal pro-B-type natriuretic peptide (NT-proBNP) or B-type natriuretic peptide (BNP), has been proposed to improve outcomes in patients with chronic HF compared with usual clinical care, especially in patients <75 years,[1–4] although individual study results were not consistent.[5–15] A more aggressive uptitration of HF medical therapy is suggested as one of the main factors responsible for the positive effect of a (NT-pro)BNP-guided management in that higher target doses of guideline-recommended HF therapy are achieved.[16] Indeed, higher doses of renin–angiotensin system

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(RAS) blockade by either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and β-blockers and higher usage of mineralocorticoid antagonists (MRAs) were reached in most (NT-pro)BNP-guided therapy studies.[5,7,10,12,15,17] This might also improve outcomes on the long term, but (NT-pro)BNP-guided studies performed to date did not extend follow-up beyond the intervention period with one exception—NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death (BATTLESCARRED) included a 2-year intervention period and an additional year of follow-up.[8] Therefore, it remains unclear whether the treatment effects persist long term after discontinuation of the (NT-pro)BNP-guided treatment strategy. The Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF) is to date largest trial in this regard, showing improved outcomes by NT-proBNP–guided therapy in patients aged 60 to 75 years, but not in those aged ≥75 years.[7] To estimate the long-term effects of NT-proBNP–guided therapy and to investigate whether the early benefit observed in TIME-CHF sustains during the long term, mainly in patients aged 60 to 74 years, we hereby report the 5-year results of NT-proBNP–guided versus symptom-guided HF therapy in TIME-CHF.

Methods

Study Design and Subjects

The TIME-CHF was a multicenter, randomized trial conducted in 15 centers in Switzerland and Germany. The trial design and methods have been published in detail previously.[18] In short, 499 patients with symptomatic HF aged ≥60 years with a left ventricular ejection fraction of ≤45% were randomized to an intensified, NT-proBNP–guided versus a standard, symptom-guided therapy. Patients were a priori stratified into 2 age groups (ie, 60–74 and ≥75 years). Guideline-recommended medication was intensified according to predefined escalation rules with the goal to reduce symptoms to New York Heart Association class II or less in the symptom-guided group and to additionally reduce NT-proBNP levels to <2× the upper limit of normal (ie, 400 ng/L in those 60–74 years and 800 ng/L in those ≥75 years) in the NT-proBNP–guided group. Study visits took place at 1, 3, 6, 12, and 18 months. Up to month 12, therapy was adjusted in collaboration with the treating general practitioners with the goal to uptitrate therapy as far as possible within 6 months. After the initial 18-month study period, 329 of 358 patients (92%) alive and participating in the study agreed to long-term follow-up (Figure I in the Data Supplement), which was conducted by telephone contact and chart review and was continued up to >5 years. End points were survival free of all-cause hospitalization, survival free of HF hospitalizations, and overall survival (excluding cancer-related death by protocol). Patients who were lost to follow-up (n=2) or withdrew from the trial declining further contact (n=18) were censored at the time of last contact. Patients who declined telephone follow-up beyond the trial period (n=29) were censored at month 18 (Figure I in the Data Supplement). The study was approved by the ethics committees of each center and each patient gave written informed consent before entering the study.

Statistical Analysis

Results are presented as frequencies (%), mean (SD), or median (interquartile range), as appropriate. RAS blockade and β-blocker doses are presented as percentage of target dose as recommended by the European Society of Cardiology HF guideline (Table I in the online-only Data Supplement). Between-group comparisons were performed using the *t* test, Mann–Whitney test, or Pearson χ^2. Survival and event-free survival was analyzed by the Kaplan–Meier method using the log-rank test to compare groups and by Cox proportional hazard regression models. Besides age groups, which were predefined by protocol, other subgroup analyses were exploratory. Interactions of the main effect were tested using Cox proportional hazard regression models correcting for the other investigated subgroup variables, that is, age, sex, New York Heart Association class, left ventricular ejection fraction, ischemic cause of HF, body mass index, comorbidities, renal failure, and baseline NT-proBNP-level, to control for confounding. Finally, we performed a landmark analysis to determine a patient's survival by response, using the 12-month uptitration phase of the study as the landmark time point. Note that in this landmark analysis, patients who die before 12 months were excluded from the analysis. Landmark analysis was performed for treatment groups and as a secondary analysis we divided patients by achieved dose of guideline-recommended HF treatment at month 12. The Cox proportional hazards assumption was tested by (1) log-minus-log survival plots, (2) comparing 2 discrete time intervals, and (3) adding a time-dependent interaction term. The models for treatment groups did not show a departure from proportionality. The models for intensification of medication, a secondary analysis, did not fulfill the assumption and therefore, Kaplan–Meier plots are presented. A 2-sided *P* value of 0.05 was considered to be statistically significant; for interaction tests a 2-sided *P* value of 0.10 was considered statistically significant. All calculations were performed with the use of the SPSS statistical package version 18.0 (SPSS Inc, Chicago, IL).

Results

Baseline Characteristics

Patient characteristics at baseline have been published in detail previously,[7] a summary is shown in Table 1. Baseline characteristics were similar between treatment groups, reflecting randomized allocation. Patients were overall elderly, predominantly men, had mainly ischemic HF with

Table 1. Baseline Characteristics

Characteristics	Symptom Guided (n=248)	NT-ProBNP Guided (n=251)	*P* Value
Age, y	77±8	76±7	0.16
Sex (women)	92 (37%)	80 (32%)	0.22
BMI, kg/m^2	25.3±4.3	24.4±4.0	0.75
NYHA class			0.61
II	63 (25%)	65 (26%)	
III	149 (60%)	157 (63%)	
IV	36 (15%)	29 (12%)	
Ischemic cause HF	149 (60%)	138 (55%)	0.28
Systolic BP, mm Hg	119±19	118±18	0.97
LVEF, %	29.7±7.9	29.8±7.7	0.87
NT-proBNP, pg/mL	4657 [2455–7520]	3998 [2075–7220]	0.12
Creatinine, mg/dL	1.33±0.42	1.32±0.45	0.69
Comorbidities ≥2	182 (73%)	181 (72%)	0.76
Renal failure	135 (54%)	140 (56%)	0.79
Atrial fibrillation	78 (32%)	82 (33%)	0.94
Diabetes mellitus	95 (38%)	77 (31%)	0.08

Data are presented as mean (SD), median [IQR], or frequency (%). BMI indicates body mass index; BP, blood pressure; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association. Adapted from Pfisterer et al[7] with permission of the publisher (American Medical Association, 2009). Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

severe symptoms as reflected by high New York Heart Association classification and high NT-proBNP levels. The presence of comorbidities was high. Background HF therapy at baseline was similar between groups, with a high use of RAS blockade and β-blockers although at suboptimal doses according to the HF guidelines.[16] Patients aged ≥75 years had more comorbidities, higher New York Heart Association classification, higher NT-proBNP, and lower left ventricular ejection fraction compared with patients aged 60 to 74 years. Also, patients in the older age group received less optimal HF medical therapy than the younger age group (Table II in the Data Supplement).

Intensification of Medical HF Therapy

At the end of the 12-month uptitration period, guideline-recommended medical HF treatment was installed and uptitrated to a greater extent in the NT-proBNP–guided group compared with the symptom-guided group (Table 2), with regard to RAS blockade, β-blockers, and MRAs. There was a nonsignificant trend toward less use of diuretics in the NT-proBNP–guided group compared with the symptom-guided group. There were no significant changes in therapy beyond the 12-month uptitration period toward the 18-month final visit (data not shown).

Although the more elderly had lower mean and achieved doses or RAS and β-blockade at 12 months compared with the relatively younger patients, NT-proBNP–guided therapy had similar positive effects on RAS and β-blockade uptitration in the younger versus the older age group. MRAs were more significantly intensified by NT-proBNP–guided therapy in the older age group, whereas NT-proBNP–guided therapy lowered diuretic usage only in the younger patients (Table III in the Data Supplement).

Table 2. HF Medical Therapy in the 12-Month Uptitration Period by Treatment Group

	Symptom Guided (n=175)	NT-ProBNP Guided (n=195)	*P* Value
RAS blockade (percentage of target dose)*			
Absolute uptitration	12.5 [0–50]	50 [0–75]	<0.001
At 12 mo, n (%)	166 (95%)	189 (97%)	0.31
Achieved dose	62.5 [50–100]	100 [50–100]	0.001
Average daily dose	81 [49–100]	87 [55–100]	0.01
β-Blockade (percentage of target dose)*			
Absolute uptitration	12.5 [0–25]	25 [0–50]	<0.001
At 12 mo, n (%)	164 (94%)	176 (90%)	0.22
Achieved dose	25 [19–100]	37.5 [25–75]	0.27
Average daily dose	32 [16–52]	37 [21–53]	0.28
MRA (spironolactone equivalent)†			
Absolute uptitration	0 [0–0]	0 [0–25]	0.013
Started during 12 mo, n (%)	23 (15%)	41 (23%)	0.03
At 12 mo, n (%)	63 (36%)	98 (50%)	0.009
Achieved dose	0 [0–25]	6.25 [0–25]	0.003
Average daily dose	2 [0–20]	12 [0–25]	0.04
Loop diuretics (furosemide equivalent)‡			
Absolute uptitration	20 [0–80]	10 [0–80]	0.60
At 12 mo, n (%)	163 (93%)	170 (87%)	0.06
Achieved dose	40 [40–80]	40 [20–80]	0.40
Average daily dose	56 [32–86]	48 [30–93]	0.15

Data are presented as median [IQR] or frequency (%). Max uptitration: maximum dose increase from baseline; achieved dose: the actual dose at the end of the uptitration period; average daily dose: the average daily dose during the uptitration period; calculated per patient separately using the daily medication data to present the actual dose that the patient received in this period. HF indicates heart failure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and RAS, renin–angiotensin system.

*Percentage of target dose as recommended by the European Society of Cardiology HF guideline,[16] see Table I in the Data Supplement.

†Dose represents spironolactone dose in milligram.

‡Dose represents furosemide equivalent in milligram (10 mg torasemide equals 40 mg furosemide).

Long-Term Outcome

During follow-up, 199 patients died (39.9%). Of those, 6 died of cancer and were censored at the time of death. Cause of death was predominantly cardiovascular.[19] A total of 254 patients (50.9%) experienced the disease-specific end point of HF hospitalization or death and 379 patients (76.0%) experienced the end point of all-cause hospitalization or death with a median follow-up of 26 months (interquartile range, 16–41).

Intensified, NT-ProBNP–Guided Therapy Versus Symptom-Guided Therapy

Hospital-free survival (Figure 1A, left) and overall survival (Figure 1C, left) were not significantly reduced by NT-proBNP–guided therapy, but there was a significant demonstrable benefit of NT-proBNP–guided therapy on the disease-specific end point of HF hospitalization-free survival (Figure 1B, left). Performing several sensitivity analyses, that is, (1) excluding patients who discontinued the study regime before 12 months (n=46), (2) treating those who were lost or withdrawn without further contact (n=20) as having died, and (3) additionally treating those who refused follow-up beyond 18 months (n=29) as having died, did not alter the results (data not shown).

Influence of Patient Characteristics on Treatment Effect

The long-term effects of NT-proBNP–guided therapy were more favorable in patients aged 60 to 74 years compared with patients aged ≥75 years (*P* for interaction 0.05 for hospital-free survival, *P*=0.06 for HF hospital-free survival, and *P*=0.09 for overall survival; Figure 2) with a significant positive effect of NT-proBNP–guided therapy on the primary end point (Figure 1A, middle) and HF hospitalization-free survival (Figure 1B, middle) in the predefined younger age group. Further subgroup analyses suggested interactions with comorbidity burden, body mass index, baseline NT-proBNP concentration, kidney disease, and sex (Figure 2).

Landmark Analysis

Baseline characteristics and 12-month clinical characteristics were similar in both treatment groups for the patients included in the landmark analysis (Table IV in the Data Supplement), besides a higher prevalence of diabetes mellitus in the symptom-guided group. Landmark analysis showed that there was

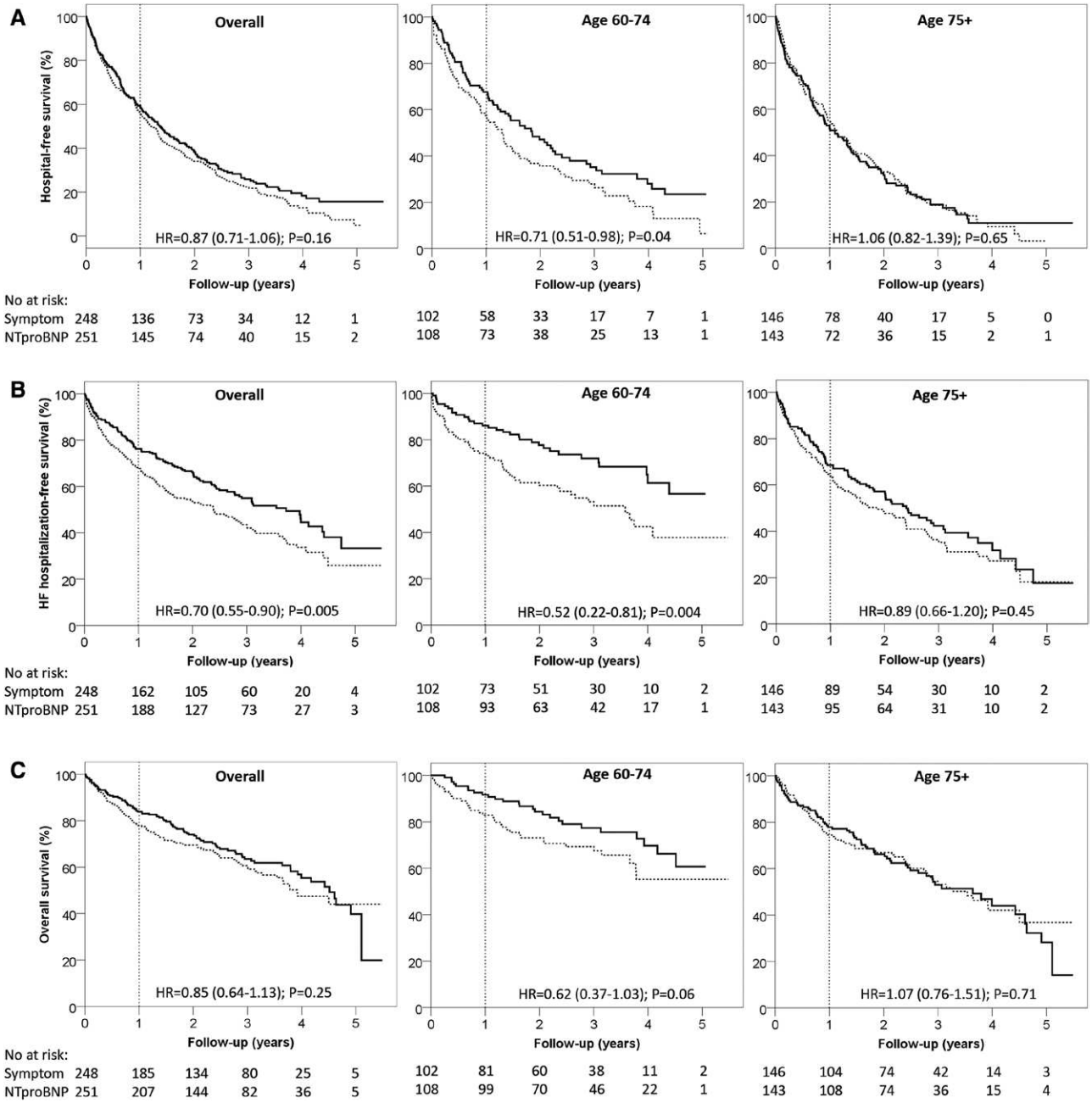

Figure 1. Kaplan–Meier curves for long-term outcome divided by treatment groups. **A**, Heart failure (HF) hospitalization-free survival; (**B**) hospital-free survival; and (**C**) overall survival. Solid line, N-terminal-pro-B-type natriuretic peptide (NT-proBNP) guided; dashed line, symptom-guided. The vertical line indicates the landmark point and the end of the 12-month uptitration period. HR indicates hazard ratio.

no significant effect of NT-proBNP–guided treatment on hospitalization-free survival (hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.63–1.04; *P*=0.10), HF hospitalization-free survival (HR, 0.76; 95% CI, 0.55–1.05; *P*=0.10), or overall survival (HR, 1.001; 95% CI, 0.68–1.48; *P*=0.99) beyond the initial 12-month uptitration period. Nonetheless, the effect observed during the first 12 months was continued (ie, not reversed) after NT-proBNP–guided therapy was ceased (Figure 1).

In the prespecified younger age group, there was a positive effect of NT-proBNP–guided therapy on the primary end point hospitalization-free survival (HR, 0.67; 95 CI, 0.45–0.99; *P*=0.046) and a nonsignificant effect on HF hospitalization-free survival (HR, 0.58; 95% CI, 0.33–1.02; *P*=0.057) but no effect on overall survival (HR, 0.77; 95% CI, 0.39–1.52; *P*=0.46) in the landmark analysis. There was no landmark effect of NT-proBNP–guided treatment on outcome in the older age group (*P*≥0.50 values for all end points). Interactions between age groups and treatment allocation were not significant (hospitalization-free survival, *P*=0.17; HF hospitalization-free survival, *P*=0.19; and overall survival, *P*=0.35).

Intensification of Medical HF Therapy and Outcome

Patients in the landmark analysis were divided according to achieved medical therapy at month 12, reflecting response to

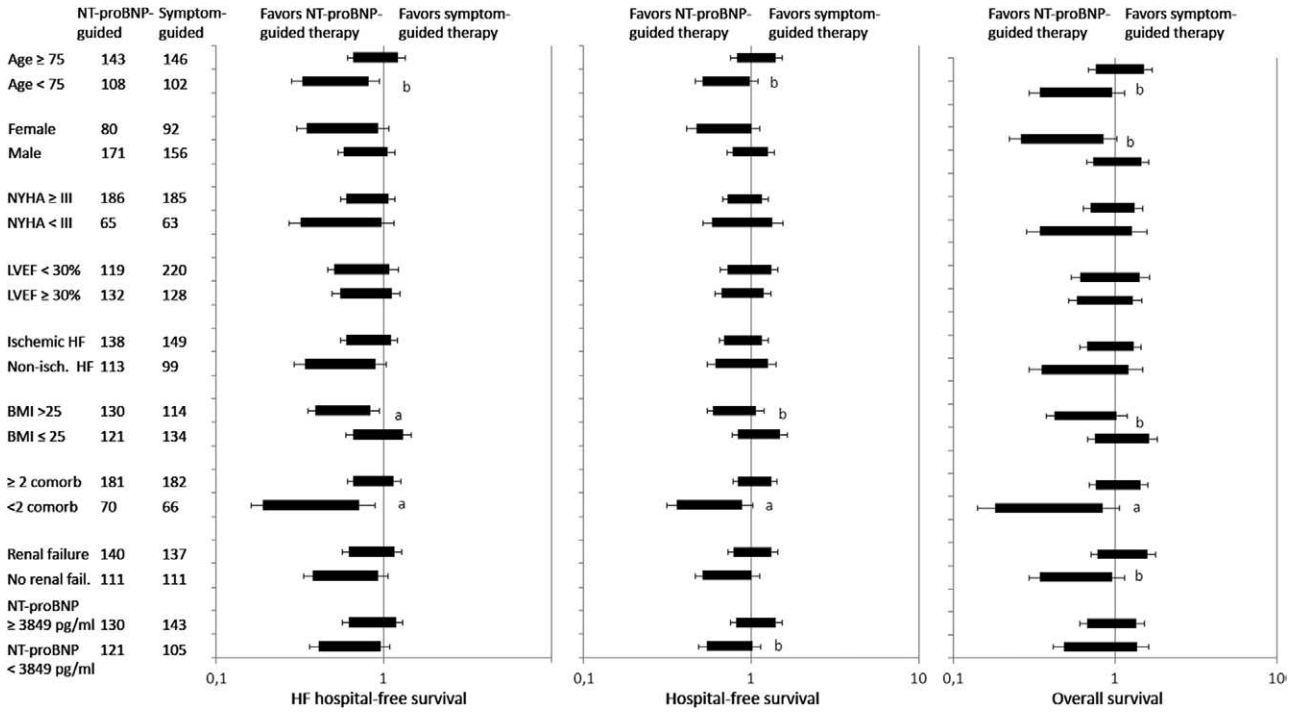

Figure 2. Interactions between patient characteristics and treatment allocation on long-term outcome. Bars indicate 95% confidence interval (CI) of the hazard ratio, error bars indicate 99% CI of the hazard ratio. Interactions: [a]*P*<0.05; [b]*P*<0.10. BMI indicates body mass index; comorb, comorbidities; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal Pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

the guided strategy. Patients with levels of RAS blockade and β-blockers at 12 months ≥50% of target dose had better HF hospitalization-free survival and overall survival compared with those with lower levels of RAS blockade and β-blockers, but there was no effect on hospitalization-free survival (Figure 3A). Results were similar when additionally considering the installation of a MRA (Figure 3B). Higher levels of medical HF therapy positively influenced outcomes in the younger age group but not in the older age group (Table V in the Data Supplement).

Discussion

The principal findings of the study are that intensified, NT-proBNP–guided therapy does not improve the primary end point of the study, whereas the positive effect of intensified, NT-proBNP–guided therapy on the disease-specific outcome observed during the intervention period persists thereafter, that is, when NT-proBNP levels are no longer measured after uptitration, resulting in an improvement of long-term survival free of HF hospitalization as compared with symptom-guided therapy in patients with HF aged ≥60 years. The persisting long-term effect was only seen in the relatively younger patients aged 60 to 74 years, confirming the early effect they experienced, but not in the more elderly. Finally, the positive and long-term effect of NT-proBNP guidance seems to be related to a more intensified use of HF medication.

During the 18-month main trial period of TIME-CHF, there was no significant effect of NT-proBNP–guided therapy on the primary end point survival free of hospitalization, although the secondary end point survival free of HF hospitalization was positively influenced in the overall population.[7] Also, patients aged 60 to 74 years of age clearly benefitted from intensified therapy with regard to both HF hospitalization-free and overall survival, whereas those aged ≥75 years did not show any benefit at all.[7] Age groups in TIME-CHF were prestratified and other trials had similar findings with regard to age,[8] but still it has to be noted that this was a subgroup analysis. In this regard, the long-term results presented here are important because the persisting and even slightly augmenting effect beyond the intervention period confirms the positive effect of NT-proBNP–guided therapy in the younger age group, whereas a regression toward the mean would point toward a chance finding.

It is important to note that the long-term outcome of our population was poor on hospitalizations and mortality. The 5-year mortality rate in TIME-CHF of 39% is comparable with that of several large registries, ranging from 31% to 49%,[20,21] showing that our population is highly representative of the real-life HF population. Previous investigations of (NT-pro)BNP-guided treatment of patients with HF have mainly reported short- or midterm results.[1,5,10,12,15,17,22,23] The BATTLESCARRED study was to date the only study that reported follow-up results ≤1 year after the intervention period,[8] showing that the positive effects of NT-proBNP–guided therapy are maintained after cessation of the guided strategy. We extend these results to 4 instead of 1 year of additional follow-up after the intervention period, showing that the initial beneficial effect remains present long term after cessation of the NT-proBNP–guided strategy. TIME-CHF applied treatment strategies for a shorter period compared with BATTLESCARRED, indicating that it might be sufficient to apply the NT-proBNP–guided strategy

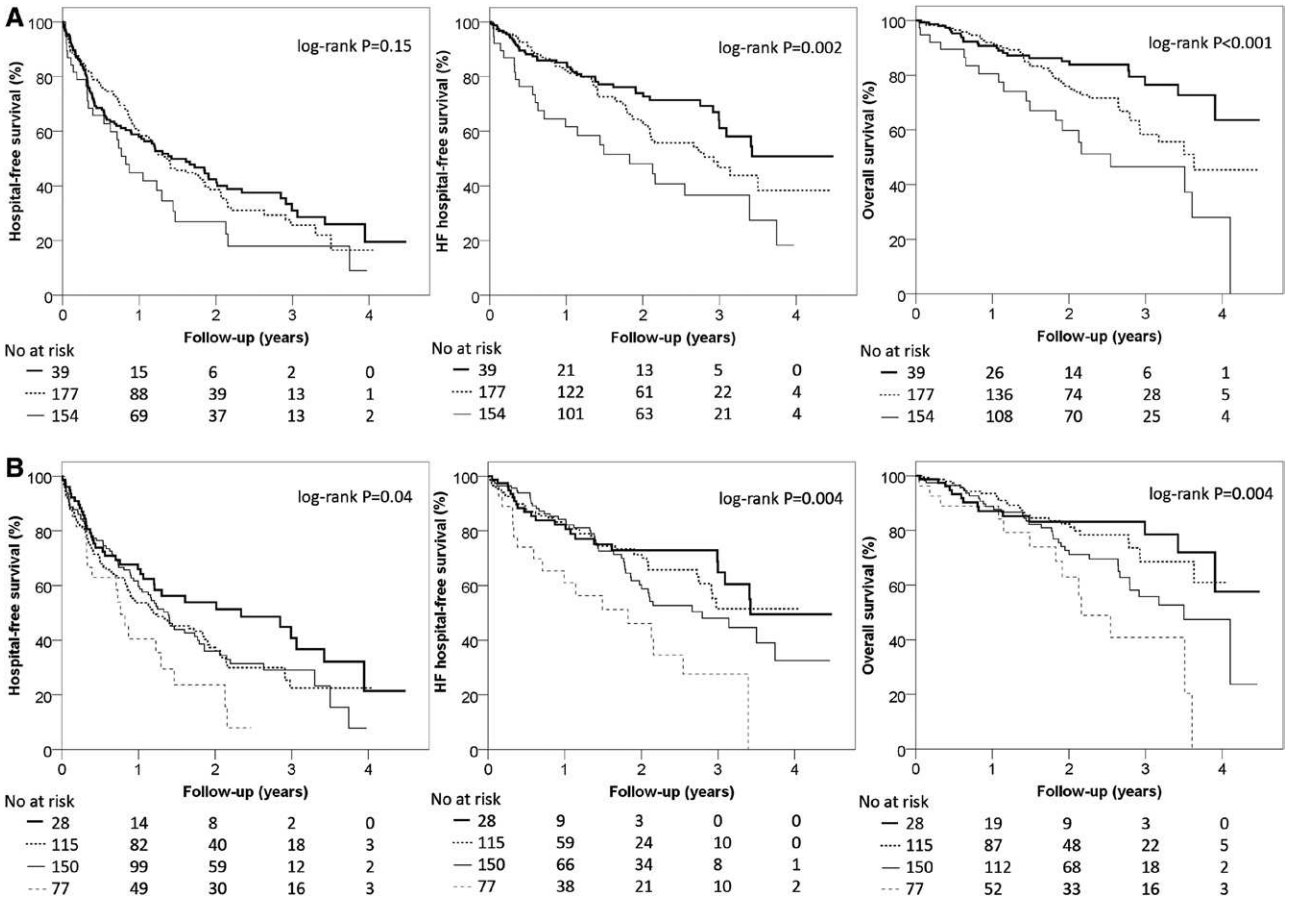

Figure 3. Kaplan–Meier curve landmark analysis by relative doses of heart failure (HF) medication. **A**, Considering renin–angiotensin system (RAS) blockers and β-blockers. Solid thick line, RAS blockade and β-blocker ≥50% target dose; dashed line, RAS blockade or β-blocker ≥50% target dose; solid thin line, RAS blockade and β-blocker <50% target dose. **B**, Considering RAS blockers, β-blockers, and mineralocorticoid antagonists (MRAs). Score consists of RAS blockade ≥50% target dose=1 point; β-blocker ≥50% target dose=1 point; MRA use=1 point. Solid black thick line, 3 points; dashed thick line, 2 points; solid black thin line, 1 points; dashed thin line, 0 points. The zero time point on the x-axis represents the 12-month landmark point.

for a shorter period to reach similar results. The protocol of TIME-CHF aimed to uptitrate medication as far as possible within 6 months, but NT-proBNP measurements were repeated after 12 and 18 months, allowing further adjustment of therapy if required. Based on our current knowledge and based on the protocol of the study, we would advise clinicians to implement a NT-proBNP–guided strategy for individualized uptitration for a limited duration of 6 to 12 months only with 1 or 2 control measurements thereafter. However, it is important to note that our results are insufficient to make definite conclusions about the best time frame. Therefore, further research is needed to assess whether a short period of individualized, biomarker-guided intensification of HF medication could improve outcome. The currently ongoing GUIDE-IT (Guiding Evidence Based Therapy Using Biomarker Intensified Treatment) trial,[24] planned to be the largest NT-proBNP–guided trial thus far, will hopefully be able to give more definite answers.

Despite general consensus on medical therapy in HF with reduced left ventricular ejection fraction,[16] there is a relative underuse and insufficient uptitration of HF medication in current clinical practice,[25,26] particularly in the elderly.[27–30] A performance improvement intervention, including education, decision support, and other support tools, could improve doses of β-blockers but not that of RAS blockade or MRAs in an outpatient setting.[26] Interestingly, patients with known BNP levels did not differ in the use of guideline-recommended HF therapies compared with those with unknown BNP levels, but patients with the highest BNP levels were less likely to be treated with RAS blockers or MRAs, whereas they are probably at highest risk of adverse outcome.[31] Thus, there is undoubtedly room for further improvement of treatment. (NT-pro)BNP-guided therapy led to more intensification of HF medication in most[5,8,10,12,15,17] but not all[22,23] guided trials. In TIME-CHF, patients who actually had more intensified HF medical therapy at 12 months had significantly better outcome compared with those with less intensified medical therapy. These results need to be taken cautiously because there might be bias, as the sickest patients are those in whom it is most difficult to intensify HF medication and landmark analysis does not take into account confounding. Still, the positive and long-term effects of NT-proBNP–guided therapy seem at least in part attributable to the achievement of more intensified HF therapy.

The lack of effect of NT-proBNP–guided, intensified treatment in the more elderly is a matter of discussion. NT-proBNP was shown previously to have important

prognostic capacity also in the elderly patients, despite a general increased concentration in older patients.[32] Therefore, we used age-dependent target concentrations in TIME-CHF, making it unlikely that NT-proBNP characteristics are causing the difference in age groups. Although current HF guidelines advise to apply therapy regardless of age and comorbidities,[16] the recommendations are mainly based on subgroup analyses[33,34] because large HF medication trials have included relatively young patients with little comorbidities and specific trials in the elderly are scarce.[35] In our study, NT-proBNP guidance led to more intensified HF medication, both in the younger and older age groups. Even more so, MRAs were intensified by NT-proBNP–guided therapy primarily in those aged ≥75 years. Despite, NT-proBNP–guided therapy failed to be effective in those aged ≥75 years and the positive effect of actual intensified therapy at month 12 was also lacking in the more elderly. This underlines the suggestion that stringent intensification of HF medication might not be most optimal in the elderly and the question should be raised whether a one-size fits all add-on therapy is really the best way to go in all patients with HF.

Limitations

Long-term follow-up was defined per protocol,[18] but separate informed consent had to be obtained. Consequently, not all patients agreed on further being contacted after completion of the first 18 months. Still, a large number of patients agreed to long-term follow-up. Long-term follow-up was conducted only by telephone and chart review and did not include symptoms or medication. Thus, there is no information on eventual changes in medication beyond 18 months. In addition, landmark analysis ignores changes in group membership after the landmark time. As such, patients who reached more intensified levels of HF medication beyond month 12 are still classified as nonresponders. Furthermore, landmark analysis is an observational data analysis because group membership is determined at the landmark time point according to response to treatment. However, confounding in landmark analysis for the randomized treatment arms was limited. Also, the landmark point was selected a priori as the uptitration period of 12 months,[18] preventing data-driven results. Moreover, by presenting both the landmark analysis next to the overall survival time results, we have incorporated the landmark analysis as a form of sensitivity analysis as recommended.[36] With regard to the analysis on the effect of actual intensification of medication, it needs to be stated that the Kaplan–Meier curves divided by medication doses at month 12 intersect, making it difficult to interpret these results and draw definite conclusions. Blinding of physicians was not able in this study design. However, an end point committee blinded to group allocation evaluated all study end points. Although the uptitration scheme was predefined per protocol, physicians treated patients according to their own discretion. Finally, subgroup analyses besides the age groups were not prestratified and should be considered hypothetical.

Conclusions

Intensified, NT-proBNP–guided therapy did not improve the primary end point on the long-term compared with symptom-guided therapy, whereas it did improve long-term survival free of HF hospitalization versus symptom-guided therapy, a secondary but disease-specific end point of the study. In the predefined age group of 60 to 74 years, clinical outcome including the primary end point was influenced positively, whereas no effects were seen in patients aged ≥75 years. Importantly, the effects of NT-proBNP–guided therapy were maintained after cessation of this strategy during the long term. Possibly, this is attributable to a more intensified HF medical therapy in the NT-proBNP–guided group as seen after completion of uptitration of medication. Further research is needed to assess whether a short period of individualized, biomarker-guided intensification of HF medication could improve outcome and whether particular groups of patients profit most from this approach.

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CLINICAL PERSPECTIVE

The role of N-terminal-pro-B-type natriuretic peptide to guide and intensify heart failure (HF) management continues to be debated. Although trial results to date are not uniform, taken altogether they suggest that N-terminal-pro-B-type natriuretic peptide–guided therapy results in intensification of medical HF therapy and may improve outcome. It remains unknown what the long-term effects are of this strategy and whether the benefits persist after the guided-strategy phase ends. This analysis of the randomized controlled Trial of Intensified versus Standard Medical therapy in Elderly Patients with Congestive Heart Failure includes 5-year follow-up and shows that N-terminal-pro-B-type natriuretic peptide–guided therapy is not effective in improving the primary trial end point. There was an apparent favorable effect on long-term HF hospitalization-free survival in patients with HF with reduced left ventricular ejection fraction, age ≥60 years, possibly attributable to more intensified medical HF therapy. The initial positive effect of N-terminal-pro-B-type natriuretic peptide–guided therapy, which was only observed in the patients aged 60 to 74 years—prestratified per protocol—did not regress to the mean in a landmark analysis starting at 12 months. Similar to the main study results, there was no effect of the intervention in patients ≥75 years. Overall prognosis remains poor (mortality rate 40%), despite near-optimal medical HF therapy. Because we included a representative elderly and highly comorbid HF population in our trial, the results presented should be generalizable.